THE U.S. DEPARTMENT OF DEFENSE PHARMACOECONOMIC CENTER

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Back Issues on the PEC Website at www.pec.ha.osd.mil

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Note from the Editor

Thanks to all the folks who signed up for the e-mail newsletter! We had a great response and are looking forward to expanding our audience in the future.

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Highlights of the August 2000 DoD Pharmacy & Therapeutics Committee Meeting

The DoD P&T Committee met 17 Aug 00 at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. Complete meeting minutes are available on the PEC Website at **www.pec.ha.osd.mil/PT_Committee.htm**. .

Major news from the meeting

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Also discussed at the meeting

- **The Advances in Medical Practice (AMP) Program:** The "best guess" is that total military treatment facility (MTF) expenditures for drugs on the AMP list will be around $47 million for fiscal year 2000 (FY00), which will use up all the FY00 AMP funds available for pharmacy. The committee decided to make no changes in the drugs covered by the AMP program until they were more certain about FY00 expenditures and AMP funding available for pharmacy for FY01. More information about the AMP program and a list of drugs reimbursed under the program is available in the minutes of the 24 February 00 meeting **(www.pec.ha.osd.mil/PT_C/ptmn0200.htm)**.
- Increased utilization indicates that the **drugs and drug classes added to the Basic Core Formulary (BCF) in Jan 00** as a result of Program Budget Decision 041 have been added to formularies across DoD.
- The committee appointed a **subcommittee to develop standard procedures for MTFs to request changes to the BCF and to propose agenda items for the DoD P&T Committee.** The subcommittee will present its recommendations at the next meeting. The point of contact for this subcommittee is MAJ Barbara Roach, the Air Force physician (internal medicine) representative at the PEC.
- The committee discussed the **controlled distribution programs for alendronate (Fosamax) 40 mg for Paget's Disease and dofetilide (Tikosyn).** Work on both these issues is continuing.
- The **NMOP preferred drug program** and the **Prior Authorization Program for the NMOP and the retail network** was also discussed during the meeting. Please see meeting minutes for further information.

Highlights of the DoD P & T Committee Meeting

17 August 2000

Ramipril selected for the Basic Core Formulary as a second long-acting ACE inhibitor

Angiotensin converting enzyme (ACE) inhibitors are known to provide significant clinical benefits at a reasonable cost. Many MTFs have added ACE inhibitors to their formularies in addition to the BCF agents (captopril and lisinopril). The purpose of adding another long-acting ACE inhibitor to the BCF was to ensure uniform availability at all MTFs of an additional agent in this category, thus hopefully promoting the use of ACE inhibitors in appropriate patients.

The decision was made in two stages: 1) consideration of the relative safety, tolerability, efficacy, and other factors pertaining to the ACE inhibitors, and 2) consideration of the weighted average daily cost per patient for each ACE inhibitor. The weighted average daily cost was derived from the frequency distribution of prescribed daily doses in DoD Military Treatment Facilities using data from the Uniformed Services Prescription Database (USPD) and the price per tablet for each strength of each ACE inhibitor based on the prices offered by pharmaceutical companies in response to a Blanket Purchase Agreement (BPA) request for price quotes issued by Defense Supply Center Philadelphia (or the DAPA price if a company did not submit a price quote).

The committee agreed that:

- Fosinopril may offer a slight safety/convenience advantage in patients with renal or hepatic failure due to its lack of dose adjustment requirements.
- There is insufficient evidence to conclude that ACE inhibitors differ significantly in their propensity to cause cough.
- All long-acting ACE inhibitors appear to be similar in efficacy for hypertension.
- Benazepril, enalapril and ramipril have the most evidence of a beneficial effect on renal disease/diabetic nephropathy.
- Enalapril and ramipril have the most extensive evidence of reduction in morbidity and mortality in patients with congestive heart failure (CHF), post-myocardial infarction (MI), or asymptomatic left ventricular (LV) dysfunction. Trandolapril has evidence of reduction in morbidity and mortality in a subset of these patients (LV dysfunction post MI). Fosinopril, quinapril, and perindopril have evidence of a beneficial effect on signs and symptoms of CHF and on disease progression, but lack mortality data. Moexipril and benazepril have little or no evidence supporting use in these patient populations.
- Ramipril appears to be the only ACE inhibitor with evidence of a reduction in the risk of stroke in patients at high cardiovascular risk.

Ramipril had the second lowest weighted average daily cost per patient, which was only $0.008 more than the lowest cost ACE inhibitor (a difference of $2.92 per patient per year). The committee concluded that ramipril offered the greatest value to DoD because its extensive evidence of proven clinical benefits for a variety of conditions outweighed its slightly higher cost. The committee decided (by a vote of 8 to 1) to add ramipril to the BCF. The ACE inhibitor class remains open on the BCF.

The committee emphasized that the addition of ramipril to the BCF is not intended to cause MTFs to delete other ACE inhibitors from their formularies or to switch patients who are already using other ACE inhibitors to ramipril.

Editor's Note: Based on the Heart Outcomes Prevention Evaluation (HOPE) study [(NEJM 2000; 342(3): 145-53 (20 Jan 00)], the FDA recently approved additional indications for ramipril to reduce the risk of stroke, myocardial infarction and death from cardiovascular causes in patients $\geq$ 55 years of age that have a history of coronary artery disease, stroke, or peripheral vascular disease or diabetes and one other cardiovascular risk factor (e.g., elevated cholesterol levels, cigarette smoking).

The ACE Inhibitor Class Review prepared by the PEC for the August 2000 meeting of the DoD P&T Committee is available on the PEC website at: **www.pec.ha.osd.mil/Updates/0005web/Oct_00_Update_Page_1.htm** (look for the link at the bottom of the page.)

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Generic Availability of ACE Inhibitors

The patent for enalapril (Vasotec; Merck) expired 22 Aug 00. Unlike many drug classes in which one generic manufacturer has rights to a 6-month exclusivity period, as many as ten generic manufacturers are likely to compete for this market, contributing to rapid price decreases. According to the FDA's "Electronic Orange Book" (www.fda.gov/cder/ob), patents for lisinopril (Zestril and Prinivil) expire Dec 01. The next ACE inhibitor to go generic is likely to be benazepril (Lotensin), with a patent expiration of Aug 03.

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Changes to the BCF

The Sarafem brand of fluoxetine, which is supplied with special packaging/labeling to support the recently approved indication for fluoxetine for Premenstrual Dysphoric Disorder (PMDD), **was excluded from the BCF listing for fluoxetine.** The committee added Sarafem to the NMOP formulary. MTFs are not required to have the Sarafem brand of fluoxetine on their formularies because:

- There are no chemical or formulation differences between Sarafem and the Prozac brand of fluoxetine. Fluoxetine (Prozac) is on the BCF.
- While Sarafem and Prozac may be the same price now, a generic form of fluoxetine may be available as soon as 2001 and may be much less expensive than Prozac or Sarafem.
- The committee is skeptical that the specialized labeling for Sarafem offers any significant incremental value over the Prozac brand of fluoxetine.

Status of oxycodone/acetaminophen on the BCF:
The committee changed the BCF listing for oxycodone / acetaminophen to state " oxycodone / acetaminophen 5/325 mg **and/or** 5/500 mg." MTFs may decide to have one or both combinations on their formularies. The previous listing required all MTFs to have both strengths on their formularies.

Status of Ortho-Novum 7/7/7 on the BCF

At the last meeting, the committee discussed removing ethinyl estradiol 35 mcg/norethindrone 0.5/0.75/1 mg (Ortho-Novum 7/7/7) from the BCF due to its high price compared to other triphasic oral contraceptives, but withdrew the decision upon learning that the product was still available from the DSCP Centrally Managed Inventory Program (the Depot) at a considerably lower price per cycle.

Ortho-Novum 7/7/7 is one of two oral contraceptive products still available through the Depot. The price of Ortho-Novum 7/7/7 through the Depot is approximately $5.56 per cycle, including surcharge, compared to $15.78 per cycle through the prime vendor program (DAPA price as of May 00). The Ortho-Novum 7/7/7 packages stocked in the Depot are clinic packs, which cannot be included under the prime vendor program.

About 64% of the estimated 274,000 cycles of Ortho-Novum 7/7/7 purchased by MTFs from Apr 99 to Mar 00 were obtained from the Depot. The DSCP product manager expects that the product will continue to be available through the Depot until at least 2002.

The committee agreed that Ortho-Novum 7/7/7 should remain on the BCF, but strongly encouraged MTFs to order the product through the Depot whenever possible. MTFs having difficulty obtaining Ortho-Novum 7/7/7 from the Depot should contact DSCP. Contact information for the DSCP Depot Program can be obtained from the DSCP website **(www.dmmonline.com**, click on "Pharmaceuticals").

Changes to the NMOP Formulary & Retail Network

NMOP Additions

The following recently approved drugs were added to the NMOP formulary. None of these drugs were added to the BCF. All of these drugs are available through the retail network.

- **Triamcinolone acetonide nasal spray (Tri-Nasal; Muro Pharma)**, approved 4 Feb 00 for treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 12 years and older. Tri-Nasal will have a quantity limit of 6 bottles (45 gm) per 90 days in the NMOP and 2 bottles (15 gm) per 30 days in the retail network, which is consistent with the established quantity limits for other nasal corticosteroids.
- **Zonisamide capsules (Zonegran; Elan)**, approved 31 Mar 00 for adjunctive treatment of partial seizures in adults 16 years and older with epilepsy.
- **Meloxicam tablets (Mobic; Boehringer-Ingelheim/Abbott)**, approved 13 Apr 00 for relief of the signs and symptoms of osteoarthritis. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that is preferential but not completely selective for cyclooxygenase-2 (COX-2). If COX enzyme selectivity is conceptualized as a spectrum, meloxicam, like nabumetone and etodolac, tends to bind more to COX-2 than cyclooxygenase-1 (COX-1), while drugs such as naproxen tend to bind more to COX-1 than COX-2. Unlike celecoxib and rofecoxib, meloxicam retains some activity at COX-1 receptors.
- The committee decided that meloxicam will be identified as a non-preferred drug (like other brand name NSAIDs) on the NMOP formulary. Meloxicam is not subject to prior authorization in the NMOP or in the retail network.
- **Pemirolast potassium ophthalmic solution (Alamast; Santen)**, approved 24 Sept 99 for prevention of itching of the eye due to allergic conjunctivitis.

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- **Testosterone 1% gel (Androgel; Unimed Pharma)**, approved 28 Feb 00 for primary hypogonadism secondary to testicular failure and hypogonadotropic hypogonadism secondary to gonadotropin deficiency.

NMOP Exclusions

Linezolid injection, tablets, and oral suspension (Zyvox; Pharmacia & Upjohn) were approved 24 Apr 00 for nosocomial and community acquired pneumonia and complicated/uncomplicated skin/skin structure infections caused by susceptible organisms, primarily aerobic gram-positive organisms, including Enterococcus faecium (vancomycin-resistant only), Staphylococcus aureus (including methicillin-resistant strains), Streptococcus pneumoniae (penicillin sensitive strains only), Streptococcus galactiae, and Streptococcus pyogenes. Because of the potential that bacterial resistance will develop if this drug is used indiscriminately, as well as the need for dispensing the drug on a more timely basis than is possible in a mail order program, the committee excluded linezolid from the NMOP formulary. Linezolid was not added to the BCF.

While the committee discussed the possibility of instituting a prior authorization program in the retail network to ensure that linezolid is used only when truly indicated, the committee decided that a delay in therapy due to the prior authorization process would pose a greater threat than the inappropriate use that might occur in the absence of a prior authorization process. MCSCs were requested to report on the usage of linezolid in their systems at the next meeting.

More Single Source Contracts in the Works

DoD and VA continue to collaborate on single source contracts for multi-source drugs, with the VA taking the lead on the majority of these contracts. Contracting efforts for two packages of generic drugs are in progress. (**Editor's note:** Contracts for some drugs in the Generic 2000 package have been awarded. See the Contract Update on Page 7).

- The **Generic 2000** package includes acyclovir, azathioprine, etodolac, furosemide, glipizide, hydroxyurea, pentoxifylline, rifampin, selegiline, and sucralfate.
- The **Generic 2000B** package includes albuterol immediate release, amitriptyline, bupropion, buspirone, carbidopa/levodopa sustained action, carisoprodol, capsicum, diclofenac, hydrochlorothiazide, imipramine, isosorbide, ketoconazole cream, meclizine, methocarbamol, prednisone, sotalol, spironolactone 50- and 100-mg, sulindac, ticlopidine, verapamil immediate release, and valproic acid.
- A **Generic 2000C** package may be developed as drugs come off VA contracts in the next six months.

Contracting Initiatives for Oral Contraceptives

As noted at the last meeting, the committee reiterated that single source contracts should be sought for each of the following oral contraceptive agents: 1) ethinyl estradiol (EE) 35 mcg / norethindrone 1 mg 2) EE 35 mcg / ethynodiol diacetate 1 mg 3) EE 30/40/30 mcg / levonorgestrel 0.05/0.075/0.125 mcg 4) norethindrone 0.35 mcg. DSCP has the lead in developing these contracts for DoD and the VA. Minutes of the May 00 DoD P&T Committee meeting **(www.pec.ha.osd.mil/PT_C/ptmn0500.htm)** contain a table of oral contraceptives, as well as details on the oral contraceptive products added to the BCF at that meeting.

Drug Classes Under Review

The DoD P&T committee reviewed a number of drug classes that may be suitable for joint DoD/VA committed use contracts. The committee supported developing joint DoD/VA contracts whenever possible, but did not wish to neglect the potential benefits of DoD-only contracts and/or pricing agreements in cases where joint contracting was impractical. The committee came to the following conclusions regarding the potential for contracting in seven drug classes as described below. The PEC has been surveying MTF providers and pharmacists for their opinions in the following drug classes.

1. **5HT1 receptor agonists for migraine ("triptans")** - The committee concluded that the oral triptans are not sufficiently interchangeable for a closed class contract because of variability in patient response to these agents. The committee decided that an oral triptan should be selected for the BCF in an open class to ensure uniform availability of one oral triptan while allowing MTFs to have additional oral triptans on their formularies. The PEC is in the process of completing a clinical review. DSCP will obtain pricing information by issuing a BPA request for price quotes to companies that market oral triptans. The committee hopes that its evaluation of the clinical and pricing information will lead to the selection of an oral triptan for the BCF at the next meeting.

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2. **Thiazolidinediones ("glitazones")** - This drug class cannot be closed because the class is too new to accurately assess the interchangeability of the drugs. The PEC is working on a clinical review to assess the need for adding one of these agents to the BCF and will make a recommendation to the committee at the next meeting. If an agent should be added to the BCF, the committee will likely advise DSCP to issue a BPA request for price quote.

3. **Oral inhaled corticosteroids** - The PEC is working on a clinical review to assess the interchangeability of these agents for a closed class contract. P&T committee members commented at the meeting that separate contracts might be needed for low-potency and high-potency agents.

Editor's Note: *Options under consideration include (but are not limited to) selecting both a high- and low-potency oral inhaled corticosteroid for the BCF in either an open or closed class.*

4. **Nasal inhaled corticosteroids** - The PEC is working on a clinical review to assess the interchangeability of these agents for a closed class contract.

Editor's Note: *Options under consideration include (but are not limited to) selection of two agents, a high-potency aqueous formulation and a metered dose (non-aqueous) formulation, for the BCF in either an open or closed class.*

5. **Fluoroquinolones** - The committee discussed a number of factors that could complicate contracting efforts in this drug class, including readiness requirements for ciprofloxacin (approved for anthrax) and regional variations in antibiotic resistance. The committee decided not to rule out the possibility of a closed class contract until the PEC completes a clinical review.

Editor's Note: *Options under consideration include (but are not limited to) selecting an oral fluoroquinolone for the BCF in either an open or closed class.*

6. **Leutinizing hormone releasing hormones (LHRHs) [leuprolide (Lupron) and goserelin (Zoladex)]** - The VA has a closed class contract for goserelin (Zoladex) for prostate cancer, but a closed class contract may not be appropriate for DoD because these drugs are less interchangeable in a patient population that includes more women and children. Lupron is indicated for prostate cancer, endometriosis, uterine fibroids and precocious puberty. Zoladex is indicated for prostate cancer, endometriosis and breast cancer. The PEC is working on a clinical review to assess the interchangeability of these agents for a closed class contract.

Editor's Note: *Options under consideration include (but are not limited to) selecting one LHRH agonist for treatment of prostate cancer for the BCF in either an open or closed class.*

7. **Non-sedating antihistamines** - Because the market share requirements in the current incentive price agreements for the non-sedating antihistamines are difficult for MTFs to achieve, the committee concluded that the incentive price agreements probably will not yield substantial cost savings for MTFs. In light of the large increase in MHS expenditures for these agents, the committee reconsidered the possibility of a closed class contract for a non-sedating antihistamine: loratadine (Claritin) or fexofenadine (Allegra). This would mean that the contracted drug would be the only non-sedating antihistamine on the BCF in a closed class and would therefore be the only non-sedating antihistamine permitted on MTF formularies.

   The committee decided that its previous objections to a closed class contract for a non-sedating antihistamine would be obviated if the following conditions are met:

   - The contract does not affect the current status or future status of loratadine or fexofenadine in regard to the NMOP formulary. This means that both loratadine and fexofenadine would continue to be available through the NMOP.
   - The contract does NOT require DoD beneficiaries who are currently taking the non-contracted drug to switch to the contracted drug.

   The committee recommended that a joint DoD/VA closed class contract should be pursued if the VA is willing to amend its contract solicitation to include the DoD requirements. Because the VA has already completed part of the contracting process for the non-sedating antihistamines, it is possible (but by no means guaranteed) that an award for a non-sedating antihistamine could be made in the near future.

Editor's Note: *The VA amended its solicitation for non-sedating antihistamines to include DoD. The solicitation is currently under protests. The PEC is working with DSCP and the VA to resolve the protests.*

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Contract Glossary

As DoD gains more experience with national pharmaceutical contracts and agreements, the terminology used to refer to them has evolved. Types of contracts and agreements include: closed class contracts, single source contracts for multi-source drug, blanket purchase agreements, and incentive price agreements.

Closed Class Contracts

In a closed class contract, MTFs must have the contracted drugs on their formulary, must not have non-contracted drugs in the drug class on their formularies, and must comply with other provisions of the contract.

A drug class may be either open or closed on the BCF. In an open drug class, MTFs must have the BCF selections on their formularies, but may also choose to have other drugs in the same drug class on their formularies. In a closed drug class, MTFs must have the BCF selections on their formularies and but are precluded from having other drugs in the same drug class on their formularies. Statins and proton pump inhibitors are the only closed drug classes on the BCF.

Single-source Contracts for Multi-source Drugs

These contracts are for a single source (brand/manufacturer) of a drug available from several manufacturers. Contracted items are usually selected from among products listed in the FDA "Orange Book" as "A-rated" generic equivalents. Contracts for single sources of "A-rated" multi-source products do not normally require prior review by the DoD P&T Committee. Specific examples are the contracts for the Geneva brand of ranitidine and the Sidmak brand of cimetidine.

In cases where drugs are not "A-rated" generic equivalents or are not eligible for listing in the Orange Book, the DoD P&T committee will review the class to decide if the drugs are interchangeable enough for any one of them to meet the needs of the vast majority of DoD patients. Examples are diltiazem extended release (not all brands are generically equivalent), and human insulin (brands differ only in method of manufacture). [Insulin cannot be listed in the Orange Book, which does not include biologicals.]

Blanket Purchase Agreements (BPAs)

BPAs are typically the result of manufacturers offering prices to DoD (or to individual MTFs or regions) that may be based on criteria agreed to by both parties (e.g., BCF or formulary listing, no formulary disadvantage relative to other competing "market basket" products). BPAs may or may not have market performance tiers as goals. With a BPA, both parties have a 30-day out option. Price reductions are effective at the beginning of the term of the BPA.

Incentive Price Agreements (IPAs)

IPAs are usually multi-tiered agreements in which prices paid for a product by individual MTFs, regions, or DoD are based on market share within a predefined market basket. Both parties must agree to the terms before the IPA goes into effect. Price reductions are typically achieved by vendor charge-back or by reductions in price for a future time period.

Notes

The DSCP website **(http://dscp103.dscp.dla.mil/dmmonline/cbu/pharmaceuticals/mghome1.htm)** contains information on all national contracts and a list of all incentive agreements that have come through DSCP for review. Copies of the incentive agreements are available from DSCP. MTFs are encouraged to submit incentive price agreements to DSCP for review by DSCP legal staff and posting on the DSCP website in order to expand availability to other MTFs.

For an explanation of how national pharmaceutical contracts are awarded and the role of the Federal Pharmacy Executive Steering Committee and the DoD P&T Committee in joint DoD/VA contracting, see the Contract Update in the July 00 issue of the Update **(www.pec.ha.osd.mil/Updates/0004web/July_00_Update_Page_8.htm)**.

Contract Update

Proton Pump Inhibitors

The DoD contract for omeprazole (Prilosec) was recently renewed, with a voluntary price reduction of approximately 21 %. The price decreases for omeprazole from $1.40 to $1.10 per capsule, effective 1 Oct 00. This is estimated to result in an additional $11.6 million in annual cost avoidance to DoD.

New strength of Cerivastatin (0.8 mg tablet)

The FDA has approved the marketing of a new 0.8 mg dosage of cerivastatin (Baycol; Bayer). The 0.8 mg tablet is not being added to the statin contract, but is expected to be available on DAPA in October at a price of $0.50 per tablet. According to pooled data in package labeling, 0.8 mg/day of cerivastatin is associated with an approximate 42% reduction in LDL cholesterol and a 9% increase in HDL cholesterol following 8 weeks of therapy. To put this in context, a 0.8 mg daily dose ($183 per year) of cerivastatin provides approximately the same percent reduction in LDL-C as simvastatin 40 mg/day ($361 per year).

Labeling also cites results of a 24-week trial that compared the percentage of patients attaining their NCEP ATP-II goal on 0.4 mg cerivastatin daily to 0.8 mg cerivastatin daily. In the group of patients with CHD particularly (target LDL-C < 100), 99/187 (53%) patients reached goal with cerivastatin 0.8 mg vs. 34/188 (24%) with cerivastatin 0.4 mg. The percentage of patients attaining goal was 65% and 72%, respectively, for patients with $\geq$ 2 risk factors (target LDL-C <130), and 79% with both 0.4- and 0.8 mg daily doses for patients with < 2 risk factors (target LDL-C < 160). New package labeling for cerivastatin is available from the Bayer website at **www.bayerus.com/pharma/products/index.html.**

Watch for more statin information in the next edition of the PEC Update!

Reminder: Statin Therapy in Combination with Gemfibrozil

All statins have an increased risk of myopathy or rhabdomyolysis when given in combination with gemfibrozil. Due to the spontaneous nature of the reporting system, it is not known whether statins differ in the risk of myopathy or rhabdomyolysis when given in combination with gemfibrozil. According to DoD prescription data, less than 3% of MTF patients receiving any statin are also receiving gemfibrozil.

In Dec 99, Bayer changed their product package insert for cerivastatin (Baycol) to state that the use of cerivastatin and gemfibrozil together is contraindicated. To date, there have been 34 reported cases of myopathy or rhabdomyolysis among the more than 87,000 MTF patients that have taken cerivastatin. Most cases were in patients receiving cerivastatin in combination with gemfibrozil. Even though the incidence appears to be low, health care providers should be aware of this drug-drug contraindication.

Re-Award of Albuterol Inhaler Contract

The contract for albuterol inhalers was re-awarded to Zenith Goldline. The contract has an effective date of 16 Nov 00. Terms of the contracts are for one year with one option year at the same price.

Item, Package Size	NDC Number	Price
Albuterol (90 mcg) MDI, 17 gm	00172-4390-18	$1.65

New Single-Source Contract Awarded for Terazosin

A contract for terazosin 1 mg, 2 mg, 5 mg, 10 mg tablets and capsules was awarded to Geneva Pharmaceuticals, with an effective date of 5 Sep 00. The contract applies to all DoD and VA activities. Terms of the contracts are for one year with option years. Please see the DSCP Pharmaceutical National Contracts Page **(http://dscp103.dscp.dla.mil/dmmonline/cbu/pharmaceuticals/natcontract.htm#terazosin)** for NDCs and prices.

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Six New National Single-Source Contracts for Six Generic Products in the "Generic 2000" Package

The base contract performance period for all these contracts is 10/1/00 - 9/30/2001, and includes four one-year options. The items and prices are as follows:

Item, Package Size	NDC Number	Package Price	Price per Each
Acyclovir (Zenith Goldline)			
200 mg caps, 100s	00172-4266-60	$ 4.74	$0.0474
200 mg caps, 500s	00172-4266-70	$22.70	$0.0454
400 mg tabs, 100s	00172-4267-60	$ 7.44	$0.0744
400 mg tabs, 500s	00172-4267-70	$35.54	$0.0711
800 mg tabs, 100s	00172-4268-60	$12.94	$0.1294
800 mg tabs, 500s	00172-4268-70	$61.65	$0.1233
Azathioprine (Mylan)			
50 mg tabs, 100s	00378-1005-01	$18.50	$0.1850
Rifampin (Geneva)			
300 mg caps, 100s	00781-2018-01	$29.38	$0.2938
Sucralfate (TEVA)			
1 gm tabs, 100s	00093-2210-01	$ 8.97	$0.0897
1 gm tabs, 500s	00093-2210-05	$42.60	$0.0852
Hydroxyurea (Richmond)			
500 mg caps, 100s	54738-0547-01	$19.74	$0.1974
Pentoxifylline (Sidmak Labs)			
400 mg tabs, 100s	50111-0609-01	$10.50	$0.1050
400 mg tabs, 500s	50111-0609-02	$51.40	$0.1028

PDTS Update on the Pharmacy Data Transaction Service

The Pharmacy Data Transaction Service (PDTS) will consolidate information for all prescriptions filled by DoD beneficiaries at military treatment facilities (MTFs), the National Mail Order Pharmacy (NMOP), and the managed care support contractor (MCSC) retail pharmacy network into one combined patient pharmacy profile maintained in a central data repository. This will enable pharmacies and/or providers to perform on-line clinical screenings of a patient's complete prescription medication history before dispensing new or refill prescriptions to a DoD beneficiary. Potential problems, such as drug-drug interactions, therapeutic overlaps, or duplicate prescriptions, can be identified and resolved without delay. PDTS is expected to allow DoD to improve the quality of its prescription service, reduce the likelihood of adverse drug reactions, and reduce pharmaceutical costs.

Beneficiaries' primary care managers and other authorized TRICARE providers will have access to the information in PDTS. Pharmacy data storage and transactions between the PDTS and other TRICARE pharmacy sites will be secure, encrypted, and meet the privacy and security guidelines of the 1996 Health Insurance Portability and Accountability Act (HIPAA).

PDTS has been designed to add no more than 6 seconds to current prescription processing times.

More Information on PDTS

"Pharmacy Data Transaction Service Will Increase Safety, Services" - September 28th News Release on the Health Affairs website (general information), available at: **www.tricare.osd.mil/newsreleases/news2000_17.htm.**

PDTS Trifold Brochure for Providers and **PDTS Information Paper** (MS Word format), available on the PEC website at **www.pec.ha.osd.mil/Updates/0005web/Oct_00_Update_Page_5.htm.**

The PDTS Customer Service Support Center (CSSC)

The PDTS Customer Service Support Center is part of the DoD Pharmacoeconomic Center (PEC), under the oversight of LTC Don DeGroff. The PEC has direct responsibility for CSSC operational functions. However, the Triservice Medical Systems Support Center (TMSSC), located at Brooks Air Force Base in San Antonio, TX, is responsible for the day-to-day operation of the center. CSSC functions include:

- Providing support for all trouble calls generated from PDTS transmissions
- Obtaining National Council for Prescription Drug Programs (NCPDP) numbers for all MTF dispensing sites
- Assisting MTFs with Drug Enforcement Agency (DEA) numbers for data cleanup
- Assisting MTFs with National Drug Code (NDC) number identification
- Assisting with processing of prescription requests for drugs requiring prior authorization
- Preparing standardized and Ad hoc management reports

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Change of Hours for the PDTS Customer Service Support Center

As of 5 Sep 00, the PDTS CSSC hours of operation have changed to:

Monday - Friday	0700 - 0100
Saturday	0900 - 2000
Sunday	0900 - 1700

All times are Eastern Standard Time.

Hours of operation will be increased as more sites are deployed. The CSSC will eventually operate 24 hours a day, 7 days a week, once PDTS is fully deployed.

How to contact the PDTS Customer Service Support Center

The CSSC can be reached at 1-800-600-9332 (option #1), DSN 240-4150 (option #1) or (210) 536-4150 (option #1.)

PDTS Deployment Schedule

Wright Patterson AFB was deployed as the alpha site for PDTS on 29 Apr 00. TriWest/Express Scripts activated PDTS on 25 July 00, Humana/Argus on 23 Aug 00, and the National Mail Order Pharmacy (NMOP) on 12 Sep 00. Both of these Managed Care Support Contractors and the NMOP are currently on line, with activation of the remaining retail pharmacy networks expected mid-October through mid-November, 2000.

At this time, deployment of PDTS in the MTFs is scheduled for December 2000, pending completion of CHCS Pharmacy enhancements (see below). Formal testing of the enhancements is scheduled for 10 through 24 Oct 00, with re-deployment to Wright-Patterson anticipated the beginning of November.

To Learn More About PDTS: Accessing the TMSSC InfoNet

Visit the CSSC on the TMSSC InfoNet at **https://infonet.tmssc.brooks.af.mil.** This is a secured site, so you will have to complete an application for access if you do not already have an account. Once your application has been approved, go to "Supported MHS Systems" and then scroll down to PDTS. The TMSSC InfoNet site can also be accessed through TMSSC's public site at **www.medsite.brooks.af.mil**.

Provider Validation Ad Hoc Report

One of the many services that the PDTS CSSC offers is to assist sites in their CHCS Data Cleanup. Currently, there is a Provider Validation Report that exists for this purpose that is not available on the Tri-Service Medical Systems Support Center (TMSSC) web site. The report is available on the PEC website at: **www.pec.ha.osd.mil/Updates/0005web/Oct_00_Update_Ad_Hoc_Report.htm**

This validation report is to assist MTFs with ensuring that all active providers have a unique provider identifier. This report will screen out all providers who have a unique identifier (SSN, DEA #, or License #) and list all prescriptions associated with providers lacking a unique identifier. The report may be rather large for some sites. A CSSC Clinical Support Coordinator is available to assist your site with mitigation strategies in order to ensure that all necessary provider information is in the CHCS database prior to PDTS activation.

If you would like help, you can run the report, spool it, and send it to the CSSC in a text format so that they can put in mitigation strategies (suggestions) on cleaning up each provider. Please e-mail your reports to **TMSSC.DEA#@tmssc.brooks.af.mil**. Once the CSSC staff is finished, they will send the report back to you with their suggested strategies. Please contact the CSSC for questions or problems with this report.

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Other Pharmacy Ad Hoc Reports

A number of other Ad Hoc reports useful for database cleanup are available on the TMSSC InfoNet site (see "Accessing the TMSSC InfoNet" on Page 10). To find the reports select "Products and Services," then "Product Catalog." The reports may be accessed by searching for a particular term (e.g., PDTS) or by selecting "Information Management Support and Training," then "Pharmacy Ad Hocs," then "Browse Pharmacy Ad Hocs." Ad Hoc reports of particular interest include the four reports listed under PDTS and the Drug NDC Comparisons report, which enables the import of files into Microsoft Access in order to identify entries with duplicate NDC numbers.

CHCS Pharmacy Enhancements

The following enhancements will be effective prior to activation of PDTS at further military sites.

Batch Printing and Interactive Screening

This will allow users to receive PDTS warnings on the screen. CHCS will wait up to 6 seconds for possible screenings to appear from PDTS (CHCS screenings are immediate) and be cleared before the user is able to enter further prescriptions. If CHCS does not receive a response back from PDTS, up to an additional 52 seconds will be allowed for a response before a "UA" (PDTS is unavailable) label is printed. This will affect New, Modified, and Renewed prescriptions. The functionality for Refill prescriptions will remain as current (Clinical Screening done in the background).

Direct printing and Interactive Screening

This will allow users to receive PDTS warnings either on the screen or on a label. This will affect New, Modified, and Renewed prescriptions. The functionality for Refill prescriptions will remain as current (Clinical Screening done in the background).

Direct Printing Scenario

Once the prescription is entered, CHCS will give PDTS up to 6 seconds to send a response back. If the response does not come back before 6 seconds, the screen will change so the pharmacy can continue to process prescriptions. CHCS will give PDTS up to an additional 9 seconds to send a response back before a label is printed.

All Host CHCS screenings will appear instantly upon File/Exit. If a PDTS screening occurs after a CHCS screening, a second Clinical Screening screen will appear automatically after the CHCS Clinical Screening is cleared.

If connectivity is lost with PDTS, any Clinical Screening that come back from PDTS after connection is restored will print automatically to a Bulletin printer as well as be stored in CHCS. The bulletin printer will be defined within the outpatient site parameters (SFM>OMM>SIT) and can **NOT** be defined as a null device. If the connection has been down for an extended period of time, the site may choose to print the PDTS bulletin report (name unknown at this time). This report will be located in the pharmacy reports menu (PRM) and may be sorted by division. The report will print by Pharmacy, Fill Date, then one patient per page. It will include the patient's name, SSN, DDS, Date/Time Rx was filled, CHCS Rx #, PDTS Rx #, PDTS Pdur warning (code), status of Rx, Fill #, Patient's work and home number. This report may be used to prioritize the calling order if patients or providers need to be contacted.

Follow-on after above fixes: Changes to CHCS to support use of the Label Print Option (LPO)

This will enable users to use the Lexmark printers to print out auxiliary labels, patient education monographs, and the prescription labels. This will also enable the site to use a robotic system for filling prescriptions. The interface may be generic so that multiple robotic systems can be utilized. (e.g., Baker APS, ScriptPro, or Optifill). The deployment schedule for PDTS has been changed so that sites currently using the LPO option will be activated towards the end of the schedule.

In the News . . .

Mark your calendars now . . . the 2001 DoD Pharmacoeconomics/Pharmacy Benefit Conference will be here before you know it!

Place: St. Anthony Hotel on the Riverwalk in downtown San Antonio, Texas

Time: January 8-10, 2001

Conference Theme: Effectively Targeting Appropriate Drug Therapy

Participants: The conference is open to federal pharmacists and providers interested in ambulatory care pharmacy, pharmacoeconomics, and DoD pharmacy issues. A large number of attendees will be Army Ambulatory Care Pharmacists (ACPs), however participants from all services are welcome! (must obtain local funding)

Agenda & Activities: A poster session has been organized to give participants the opportunity to highlight pharmacy activities at their facility. All attendees are encouraged to present a poster.

Selected Educational Sessions

- Update on DOD Pharmacy Benefit Management Issues
- ACP Core Duties: Success Stories
- Poster Display Reception and "Best Demonstrated Practices"
- Evidence-Based Evaluation of COX-1 and COX-2 Inhibitors
- Evidence-Based Evaluation of the Statins
- Evidence-Based Treatment of Allergic Rhinitis
- New Drugs of 1999-2000
- What I Really Need to Know About Statistics
- Effective Techniques in Data Presentation
- Importance of Persuasion and Influencing Key Persons (Interactive Audience Discussion)
- Tips for Effective Communication
- Workshop Exercise*:* Three person teams will review a case study on COX inhibitors, statins or treatment of allergic rhinitis and prepare a brief presentation using key statistical information, data presentation techniques, and effective communication tips

A list of all conference activities is available in the tentative agenda for the conference, available on the PEC website at: **www.pec.ha.osd.mil/Updates/0005web/Oct_00_Update_Page_6.htm.**

Point-of-Contact: Anyone interested in attending the conference or obtaining more information should contact Jill Williams, The University of Texas at Austin, College of Pharmacy, at (512) 471-4512 or e-mail: **williamsj@mail.utexas.edu**. The PEC point-of-contact is: Eugene Moore, Pharm.D. at (210) 295-9645 or DSN 421-9645 or e-mail: **Eugene.Moore@amedd.army.mil**.

Registration Deadlines: Meeting slots are limited, so early registration is recommended. The registration deadline for hotel accommodations is 1 Dec 00. Please keep this date in mind to take advantage of the specially contracted government rate.

Meeting slots are limited, so early registration is recommended!

The TRICARE Help E-Mail Service (THEMS)

- THEMS is an e-mail resource whose sole purpose is to answer beneficiary inquiries regarding the TRICARE benefit—including pharmacy benefit inquiries. Persons using the service will receive an initial response from THEMS administrative staff within one business day to let them know which TRICARE expert has been assigned to answer their question. In some cases, inquirers will receive a reply to their question the same day, and persons with more complex questions can expect at least a preliminary reply within a week. Personal information is kept confidential. THEMS is designed to answer benefit questions. Patients with health care questions are referred to health care providers.
- The e-mail address for THEMS is **TRICARE_help@amedd.army.mil.**

Flu News

Anticipated Delay in Flu Vaccine Availability

Shortage of Flu Vaccine: CDC Information

In July, the Centers for Disease Control and Prevention (CDC) announced that it was likely that supplies of flu vaccine would be reduced or delayed across the United States for this year's flu season. As of 6 Oct 00, the CDC stated that it was likely that supplies will be delayed but that sufficient flu vaccine should be available for this flu season. Although the CDC no longer anticipates a severe flu vaccine shortfall, vaccine delays are expected to hamper influenza vaccination efforts. The CDC Advisory Committee on Immunization Practices (ACIP) has recommended that initial priority be given to vaccinating persons at high risk of complications associated with influenza and health care workers (to stop the potential spread to vulnerable persons) and that mass vaccination campaigns should be scheduled later in the season as availability of vaccine is assured. They also recommend that high risk persons should receive pneumococcal vaccination early in the influenza season, since this will confer substantial protection from secondary bacterial pneumonia, a major complication of influenza.

The most recent information from the CDC about ACIP recommendations and other preparations for this flu season is reported in the CDC's 6 Oct 00 Morbidity and Mortality Weekly Report [MMWR 49(39);888-892], available at: **www.cdc.gov/mmwr/preview/mmwrhtml/mm4939a3.htm**. A link to this report is also available on the CDC's Influenza Prevention and Control page **(www.cdc.gov/ncidod/diseases/flu/fluvirus.htm)**, along with CDC press releases, information about anticipated shortages, and recommendations of the Advisory Committee on Immunization Practices (ACIP).

ACIP recommendations for prevention of pneumococcal disease have been published in MMWR:

- *Preventing Pneumococcal Disease among Infants and Young Children*. MMWR 49(RR09):1-38 (October 6, 2000), available at: **www.cdc.gov/mmwr/preview/mmwrhtml/rr4909a1.htm**
- *Prevention of Pneumococcal Disease.* MMWR 46(RR08):1-24. (April 4, 1997), available at **www.cdc.gov/mmwr/preview/mmwrhtml/00047135.htm**

DoD Vaccine Supplies and Health Affairs Policy

CDC recommendations do not specifically address military readiness. Because delays in vaccine availability are expected to cause functional shortages in flu vaccine across the United States, the Joint Preventive Medicine Policy Group (JPMPG) has adopted the CDC and ACIP recommendations and developed a uniform immunization priority plan for DoD that attempts to balance optimal military readiness with DoD's obligation to protect beneficiaries at high medical risk. MTFs and operational force surgeons should prioritize administration of flu vaccine based on the JPMPG recommendations. The policy memorandum may be accessed on the TRICARE website at **www.tricare.osd.mil/policy/flu_poli.pdf.**

Antivirals for Influenza

Although the influenza vaccine remains the primary method of flu prevention, antiviral drugs may be useful in selected patient populations. However, even in the case of an influenza vaccine shortage, the CDC and ACIP do not support routine and widespread use of antiviral drugs as chemoprophylaxis because this strategy is untested, expensive, and could result in large numbers of persons experiencing adverse effects.

Treatment

Treatment of otherwise healthy persons already exhibiting influenza symptoms with antiviral drugs has been shown to shorten the duration of flu symptoms by 24 to 36 hours *if started within 48 hours of symptoms.* There is no evidence that antivirals prevent influenza complications (e.g., bacterial or viral pneumonia or exacerbation of chronic disease). Evidence for the effectiveness of the four available antiviral drugs approved for treatment of influenza (amantadine, rimantadine, zanamivir and oseltamivir) is based principally on studies of patients with uncomplicated influenza. The effectiveness of antivirals for treatment of influenza in persons at high risk for serious complications of influenza is unclear. Studies of the

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efficacy of any of the four drugs for treatment in children are limited. Amantadine and rimantadine are effective only against influenza A, while zanamivir and oseltamivir are effective against both influenza A and B.

Prevention

At this time, only amantadine and rimantadine are approved for the prevention (prophylaxis) of influenza. Amantadine (available in the U.S. since 1976) and rimantadine (available in the U.S. since 1993) can reduce the severity and shorten the duration of type A influenza, and have proven useful for influenza outbreaks (e.g., in long-term care facilities). However, the use of amantadine and rimantadine has been associated with adverse central nervous system (CNS) side effects (in 12% and 6% of patients, respectively). The incidence of CNS side effects is more frequent in elderly patients and dose adjustment is required. Amantadine and rimantadine are available in tablet and syrup formulations.

The newer influenza antiviral drugs, the neuraminidase inhibitors zanamivir (Relenza) and oseltamivir (Tamiflu), which became available in 1999, have not been approved for the prevention of influenza, but appear to be effective for this purpose. (Both manufacturers have submitted applications to the FDA for this indication.) Zanamivir is available as an inhaler, which requires patient education and has been reported to cause bronchospasm in patients with underlying respiratory disease. Oseltamivir is available in a capsule formulation.

CDC Recommendations for the Use of Antiviral Agents for Influenza

As part of the 2000 CDC *Recommendations for the Prevention and Control of Influenza* [MMWR 49(RR03):1-38 (April 14, 2000), available at: **www.cdc.gov/epo/mmwr/preview/mmwrhtml/rr4903a1.htm**], the ACIP has identified clinical situations in which antivirals should be considered for prevention of influenza:

- **Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun:** When influenza vaccine is given while influenza A viruses are circulating, prophylaxis with amantadine or rimantadine should be considered for persons at high risk during the time from vaccination until immunity has developed (may be as long as 2 weeks in adults). Children receiving influenza vaccine for the first time can require as long as 6 weeks of prophylaxis (4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose)

- **Unvaccinated Persons Who Provide Care to Those at High Risk:** To reduce the spread of virus to persons at high risk during community or institutional outbreaks, prophylaxis with amantadine or rimantadine during peak influenza A activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. If an outbreak is caused by a variant strain of influenza A that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

- **Persons Who Have Immune Deficiency:** Prophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with human immunodeficiency virus (HIV), especially those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if amantadine or rimantadine chemoprophylaxis is administered.

- **Other Persons:** Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated.

- **Control of Influenza Outbreaks in Institutions**: When institutional outbreaks occur, chemoprophylaxis should be administered to all residents -- regardless of whether they received influenza vaccine during the previous fall -- and should continue for at least 2 weeks or until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff who provide care to persons at high risk. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that is not well matched by the vaccine.

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FDA Advisory on the Use of Antiviral Agents for Influenza

On January 12, 2000, the Food and Drug Administration issued an public health advisory emphasizing that physicians should 1) always consider the possibility of primary or secondary bacterial infection when making treatment decisions for patients with suspected influenza, and to 2) use special caution if prescribing zanamivir (Relenza) to patients with underlying asthma or chronic obstructive pulmonary disease. The advisory is available at: **www.fda.gov/cder/drug/advisory/influenza.htm**.

Other Key Points from the CDC Recommendations

- Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in up to approximately one third of patients when either amantadine or rimantadine is used for therapy and can replace sensitive strains within 2-3 days of starting therapy). Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses. Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, especially after 5-7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge.

- To limit the potential transmission of drug-resistant virus during institutional outbreaks, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

- When determining the timing and duration for administering amantadine or rimantadine for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, amantadine or rimantadine prophylaxis should be taken only during the period of peak influenza activity in a community.

- The appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can help reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because some bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated if suspected. In addition, bacterial infections can occur as a complication of influenza.

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Comparison of Antiviral Drugs Available for Influenza*

Description	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Trade Name (Manufacturer)	Symmetrel® (Endo Pharma); multiple generics	Flumadine® (Forest Pharma)	Relenza® (Glaxo-Wellcome)	Tamiflu® (Roche)
Dosage forms	100 mg tab, 50 mg/5 mL syrup	100 mg tab, 50 mg/5 mL syrup	Diskhaler™ inhalation device	75-mg capsule
Flu virus(es) affected	influenza A	influenza A	influenza A & B	influenza A & B
Administration	oral	oral	oral inhalation	oral
Ages approved for treatment	≥1 year	≥14 years**	≥12 years	≥18 years
Ages approved for prevention	≥1 year	≥1 year	not approved for prevention	not approved for prevention
Usual adult regimen: treatment & prophylaxis	**Treatment:** 200 mg/day (100 mg twice daily) **Prophylaxis:** 200 mg/day (100 mg twice daily) To reduce emergence of antiviral drug-resistant viruses, discontinue as soon as clinically warranted, generally after 3-5 days of treatment or within 24-48 hours after disappearance of signs and symptoms	**Treatment:** 200 mg/day (100 mg twice daily) **Prophylaxis:** 200 mg/day (100 mg twice daily)	**Treatment:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days Recommended treatment duration 5 days	**Treatment**: 75 mg twice daily for 5 days
Dosing in special populations	**Elderly** Daily dose for persons ≥65 years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For some elderly persons, the dose should be further reduced. **Impaired Renal Function** Dosage reduction recommended for patients with creatinine clearance ≤50 mL/min/1.73m^2. Careful monitoring needed. See packet insert recommendations **Liver Disease** No increase in adverse reactions observed among persons with liver disease. Rare instances of reversible liver enzyme elevations reported; no specific relationship established	**Elderly** For elderly nursing home residents, reduce to 100 mg/day for prophylaxis or treatment. For other elderly persons, further studies needed to determine optimal dosage, however, consider 100 mg/day for all persons ≥65 years who experience side effects on 200 mg/day. **Impaired Renal Function** Dosage reduction to 100 mg/day recommended for patients with creatinine clearance ≤10 mL/min. Careful monitoring needed. **Liver Disease** Dosage reduction to 100 mg/day recommended for persons with severe hepatic dysfunction	**Elderly** No dosage reduction recommended on the basis of age alone. **Impaired Renal Function** Limited data Based on pharmacokinetic studies, the manufacturer recommends no dose adjustment for a 5-day course of treatment for patients with mild-to-moderate or severe renal impairment **Liver Disease** Not studied	**Elderly** No dosage reduction recommended on the basis of age alone. **Impaired Renal Function** Serum concentrations of the active metabolite increase with declining renal function. Dosage reduction to 75 mg once daily is recommended for patients with creatinine clearance < 30 mL/min. No data available concerning the safety or efficacy of oseltamivir in patients with creatinine clearance < 10 mL/min. **Liver Disease** Not studied
Pediatric dosing (from ACIP recommendations)	**Amantadine:** **<1 year:** not adequately evaluated **1-9 years:** ACIP recommended dose: 5 mg/kg/day, not to exceed 150 mg/day **≥10 years**: approved dosage 200 mg/day (100 mg twice a day). Children weighing <40 kg, regardless of age: recommended dose 5 mg/kg/day	**Rimantadine:** **<1 year:** use not adequately evaluated **1-9 years:** one or two divided doses at a dosage of 5 mg/kg/day, not to exceed 150 mg/day **≥10 years:** approved dosage 200 mg/day (100 mg twice a day). Children weighing <40 kg, regardless of age: recommended dose 5 mg/kg/day	**Zanamivir:** Not approved for use in children aged <12 years. See adult dose for adolescents ≥ 12 years	**Oseltamivir:** Not approved for use in persons aged <18 years

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Comparison of Antiviral Drugs Available for Influenza* (continued)

Description	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Safety & Tolerability	Incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) higher with amantadine than rimantadine. In a 6-week study of prophylaxis among healthy adults, incidence of at least one CNS symptom was 13%, 6%, and 4%, with amantadine (200 mg/day), rimantadine (200 mg/day) and placebo, respectively. A study in elderly persons also demonstrated fewer CNS side effects with rimantadine than amantadine. Gastrointestinal side effects in approximately 1%-3% of persons taking either drug, vs. 1% with placebo. Increased incidence of seizures reported among patients with a history of seizure disorders Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, especially CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase incidence of adverse CNS reactions. No clinically significant interactions between rimantadine and other drugs identified.		A higher incidence of > 20% decline in FEV-1 or peak expiratory flow rates noted with zanamivir in clinical trials. During postmarketing surveillance, cases of respiratory function deterioration following inhalation of zanamivir reported among patients with underlying asthma or chronic obstructive pulmonary disease). No clear evidence available regarding safety or efficacy in persons with underlying respiratory or cardiac disease or complications of acute influenza Other adverse events similar to placebo in clinical trials. No known drug interactions reported, and no clinically important drug interactions predicted on the basis of in vitro and animal data. Limited clinical data available.	Nausea and vomiting reported more frequently with oseltamivir than placebo (9-10% vs. 3-6%). Few persons discontinued treatment because of these symptoms. Nausea and vomiting might be less severe if oseltamivir taken with food Because oseltamivir and its active metabolite are excreted in the urine by glomerular filtration and tubular secretion, potential exists for interaction with other agents excreted by this pathway (e.g., oseltamivir and probenecid resulted in reduced clearance and increased plasma levels of the active metabolite). Limited clinical data available.
Special populations	No clinical studies with any of these drugs. Only two cases of amantadine use for severe influenza illness during the third trimester have been reported. Both amantadine and rimantadine have been shown in animal studies to be teratogenic and embryotoxic when administered at very high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see package inserts).			
Efficacy: treatment	When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness, by approximately 1 day.			
Efficacy: prophylaxis	Amantadine and rimantadine are approximately 70%-90% effective in preventing illness from influenza A infection. Can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza viruses; some persons will develop protective immune responses to circulating influenza viruses. Neither amantadine nor rimantadine interfere with antibody response to the vaccine. Both drugs have been studied extensively in nursing home populations as a component of influenza outbreak control programs		Zanamivir and oseltamivir not approved for prophylaxis, but appear to be similarly effective (82-84%) in preventing febrile, laboratory-confirmed influenza illness in community-based studies. Experience with prophylactic use in institutional settings or in patients with chronic medical conditions is limited. Zanamivir has not been found to impair the immunologic response to influenza vaccine. No influenza vaccine interaction study has been conducted with oseltamivir, but treatment with oseltamivir did not impair antibody response to influenza infection.	
Approximate cost to DoD per 5-day course of therapy **(assumes 5 days of treatment; DAPA prices as of 9/00))**	**Amantadine: $0.52** (at DoD/VA contract price for Invamed generic)	**Rimantadine (Flumadine): $6.80**	**Zanamivir (Relenza): $26.76**	**Oseltamivir (Tamiflu): $32.30**

* compiled from the *2000 CDC Recommendations for the Prevention and Control of Influenza.* MMWR 49(RR03):1-38 (April 14, 2000), available at: **www.cdc.gov/epo/mmwr/preview/mmwrhtml/rr4903a1.htm**.

** many experts consider rimantadine appropriate for treatment in children